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EXAMINER	
MOHAMED, ABDEL A	

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1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,355	SCHUBERT ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-86* is/are pending in the application.

4a) Of the above claim(s) *54-86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGEMENT TO THE AMENDMENT TO THE SPECIFICATION, REMARKS AND DECLARATION FILED UNDER RULES 1.131 AND 1.132

1. Applicant's amendment to the specification, remarks and declaration filed 02/04/09 under 37 CFR Rules 1.131 and 1.132 are acknowledged, considered and entered. Claims 44-86 are pending in the application of which claims 54-86 are withdrawn as non-elected inventions for the reasons of record and Applicant is required to cancel the non-elected inventions (i.e., claims 54-86) in the next communication. The objection to the specification and drawings are withdrawn in view of Applicant's amendment and remarks filed 12/12/08 (and again on 02/04/2009). However, the rejection under 35 U.S.C. 102(e) over the prior art of record is maintained for the same reasons set forth in the previous Office action.

CLAIMS REJECTION-35 U.S.C. § 102(e)

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 44-53 remain rejected under 35 U.S.C. 102(e) as being anticipated by Schubert et al (Pub. No. US 2004/0106539 A1) Cited by Applicant on IDS filed 4/13/06.

Applicant's arguments and the declaration filed 02/04/09 have been fully considered but they are not persuasive. Applicant's arguments and the declaration submitted under 37 CFR Rules 1.131 and 1.132 states that We, Ulrich Schubert, Hans Will and Huseyin Sirma declare the followings: in which Ulrich Schubert alleges that he is the **only** inventor of the subject matter of independent claim 44 (paragraphs 5 and 6). The instant specification have 3 co-inventors and it is not clear to the Examiner the role of other two co-inventors since Ulrich Schubert claims that he is the sole inventor of claim 44, and to the extent the claimed subject matter appears in '539 Patent application, it represents his work and not the work of others (i.e., co-inventors of the instant specification). Thus, the declaration submitted under 37 CFR Rules 1.131 and 1.132 does not establish that the prior art reference is by the instant inventors. The Declaration says that there is one inventor, and therefore it is by another. Hence, the prior art rejection is maintained for the same reasons as set forth in the previous Office action as reiterated below.

The elected claims are drawn to an agent for inhibiting at least one of release, maturation and replication of a member of the *Flavivirdae* family selected from *Flavivirus* wherein the agent comprises, as an active component, at least one proteasome inhibitor in a pharmaceutical preparation (claim 44), wherein the agent is used for the treatment and prophylaxis of HCV-induced hepatitis, falvivirus-induced fever (claim 45), wherein the proteasome inhibitor is a substance which affects the activities of the ubiquitin/proteasome pathway; which specifically affects the enzymatic activities of the complete 26S proteasome complex; and which specifically affects the enzymatic activities of the free 20S catalytically active, proteasome complex, which is not assembled with regulatory subunits (claim 46), wherein the proteasome inhibitor is taken up by higher eukaryotic cells and, after having been taken up into a cell, interacts with the catalytic

subunits of the proteasome, and, in connection with this, blocks at least some of the proteolytic activities of the proteasome within the 26S or the 20S proteasome complex (claim 47), wherein in addition to proteasome inhibitors, the pharmaceutical preparation also comprises at least one further agent which inhibits the cellular ubiquitin system, such as the activities of the ubiquitin-conjugating enzymes and/or of the ubiquitin-hydrolyzing enzymes (claim 48), wherein the proteasome inhibitor is administered in various mode of administrations as recited in claim 49, wherein the proteasome inhibitor is produced from various sources as recited in claim 50, the boric acid derivatives of modifies aldehydes (claim 51), epoxomycin (claim 52) and PS-341 (claim 53).

The reference of Schubert et al ('539) discloses agents for the treatment of viral infections, in particular, infections with hepatitis of acute and chronic HCV such as Flavivirus. Said agents inhibit the release, maturation and replication of hepatitis virus among others viruses. In the example, hepatitis virus has been shown that the proteasome inhibitors (i.e., active component of the claimed invention) block the release of virus particles and the infectiousness of the released viral particles and thus the production of the viruses. The proteasome inhibitors affect the activities of the ubiquitin/proteasome pathway, in particular the enzymatic activities of the 26S and 20S proteasome complexes (See e.g., abstract, ¶ 0002, 0005, 0006 and particularly 0060).

The '539 discloses a composition comprising a proteasome inhibitor and a pharmaceutically acceptable carrier, wherein the proteasome inhibitor is a boric acid derivative. The inhibitor of '539 contains a boric acid radical, specifically dipeptidyl boric acid derivatives, more specifically the compound pyranosyl-phenyl-leucinyl-boric acid, referred to as "PS-341".

This is further evidenced by Applicant's disclosure in the instant specification on ¶ 0011 by stating another, and very potent, class of synthetic proteasome inhibitors are boric acid peptide derivatives, in particular the compound pyranosyl-phenyl-leucinyl-boric acid, which is named "PS-341". PS-341 is very stable under physiological conditions and is bio-available following intravenous administration.

The proteasome inhibitors of '539 is a synthetic substance. Additionally, the composition of the reference's is in a formulation that is suitable for various mode of administrations such as for oral, intravenous, intramuscular, subcutaneous, etc. (See e.g., ¶ 0076 and claim 6). Further, the '539 notes that the composition blocks peptide-hydrolyzing activity within 26S or 20S proteasome complexes (See e.g., ¶ 0073). Additionally, as a proteasome inhibitor, the composition of '539 would necessarily inhibits, regulates or affects a ubiquitin proteasome pathway; affects enzymatic activity of a complete, 26S proteasome complex, or a free, catalytically active 20S proteasome structure not assembled with a regulatory subunit; and be taken up by eukaryotic cells and interacts with a catalytic proteasome subunit for all those properties are inherent of proteasome inhibitors (See e.g., ¶ 0072-0079, 0082, 0084, 0087 and 0091-0092).

It is noted that independent claim 44 is directed to a pharmaceutical formulation and claim 45 depends from claim 44, however, claim 45 (and dependent claims thereof i.e. claims 46-53) contain an intended use recitation "used for the treatment and prophylaxis of HCV-induced hepatitis, flavivirus-induced fever", the cited reference above does not disclose the intended use of the product/composition for the treatment of flavivirus-induced fever, although, the preamble of claim 1 of '539 states a composition for treating viral infection, characterized in

that it contains at least one proteasome inhibitor as active component and in claim 32 the use of proteasome inhibitors for treating/controlling/preventing HCV-induced liver carcinomas and in claim 33 for HCV infection which may encompass the claimed falvivirus-induced fever; nevertheless a statement of usefulness or contemplated use of a claimed compound or composition in a claim is usually given little weight in distinguishing over the prior art. *In re Maeder et al.* (CCPA 1964) 337 F2d 875, 143 USPQ 248; *In re Riden et al.* (CCPA 1963) 318 F2d 761, 138 USPQ 112; *In re Sinex* (CCPA 1962) 309 F2d 488, 135 USPQ 302. Further, it is well established that the intended use of a compound (e.g., a polypeptide or a protein or a glycoprotein) does not impart patentability to the compound. *In re Spada,* 911 F.2d 705, 15 USPQ2d 1655 (Fed. Cir. 1990) (The discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, can not impart patentability to claims to the known composition); *In re Pearson*, 494 F.2d 1399, 1403, 181 USPQ 641, 644 (CCPA 1974) (intended use of an old composition does not render composition claims patentable); *In re Zierden*, 411 F.2d 1325, 1328, 162 USPQ 102, 104 (CCPA 1969).

Thus, sufficient evidence of similarity is deemed to be present between the instantly claimed invention of claims 44-53 and the prior art teachings which clearly discloses agents for the treatment and prophylaxis of viral infection which encompasses HCV-induced hepatitis, flavivirus-induce fever as disclosed in the abstract, ¶ 0002, 0005, 0016, 0060, 0071-0075, 00077-0079, 0082, 0087, 0091-0092 and claims 1-9, 11-14 and 32-34. Therefore, in the absence of evidence to the contrary or specific structural limitations, the claimed agents for treating flavivirus infections thereof as taught by the reference anticipates claims 44-53 as drafted.

The followings are new grounds of objections and rejections.

OBJECTION OF THE CLAIM

3. Claim 53 is objected because of the following informalities. Claim 53 recites "….selected from…" because it is not clear if Applicant intends a Markush format. The Office recommends using the phrase".....selected from the group consisting of....." in listing species to ensure the Markush group is "closed".

CLAIM REJECTION-35 U.S.C. 112 2nd PARAGRAPH

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 48-49 and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 48, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 49 is indefinite because it is not clear if the list of administration forms after "i.e." is intended to be open or limiting. For the purpose of examination, the claim is treated as open. Appropriate clarification is required.

Regarding claim 51, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

CLAIMS REJECTION-35 U.S.C. 102(b)

(b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 44-47, 49-51 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Adams et al (Cancer Research, Vol. 59, pp. 2615-2622, June 1999) Cited on IDS filed by Applicant on 04/13/06.

The claims are directed at a composition comprising a proteasome inhibitor and a pharmaceutical preparation thereof, wherein the proteasome inhibitor is a boric acid derivative. The claim requires that the inhibitor inhibits, regulates, or influences an ubiquitin proteasome pathway. The claims require that the inhibitor influences enzymatic activity of a complete, 26S proteasome complex, or a free, catalytically active 20S proteasome structure not assembled with a regulatory subunit. The claims also require that the inhibitor be taken up by eukaryotic cells and interacts with a catalytic proteasome subunit, and blocks at least one trypsin, chymotrypsin or postglutamyl peptide-hydrolyzing activity within the 26S or 20S proteasome complex. Additionally, the claims require that the composition be in a form suitable for oral, intravenous, intramuscular or subcutaneous use; the proteasome inhibitor be a naturally occurring substance, a chemically modified natural substance, a synthetic substance, or a substance produced via recombinant means. The claims require that the proteasome inhibitor contains a boric acid radical, which is later limited to dipeptidyl boric acid derivatives, which is further limited to N-pyrazinecarbonyl-L-phenylalanine-L-leucine-boric acid.

Additionally, it is noted that the claims contain an intended use recitation, "useful for treatment and prophylaxis of HCV-induced hepatitis' falvivirus-induced fever, hemorrhages, leucopenia, thrombocytopenia, diarrheal diseases encephalitis or pestivirus-induced diseases.

The reference of Adams et al teaches a composition comprising a proteasome inhibitor and a pharmaceutical preparation thereof, wherein the proteasome inhibitor is a boric acid derivative. [Lines 1-22, left column, page 2619.] The inhibitor of Adams et al contains a boric acid radical, specifically dipeptidyl boric acid derivatives, more specifically, N-pyrazinecarbonyl-L-phenylalanine-L-leucine-boric acid. In the instant, Adams et al. refers to N-pyrazinecarbonyl-L-phenylalanine-L-leucine-boric acid as PS-341. The proteasome inhibitor of Adams et al is a synthetic substance. Additionally, the composition of Adams et al is in a form that is suitable for oral, intravenous, intramuscular and subcutaneous. Further, most of the PS series in claim 53 are disclosed in Table I of Adams: PS-273, PS-293, PS-296, PS-303, PS-321, PS-324, PS-341, PS-325, PS-352, PS-383.

Moreover, Adams et al notes that the composition blocks chymotrypsin peptide-hydrolyzing activity within the 26S or 20S proteasome complex. [Last full paragraph, 2nd column, page 2615]. Additionally, as a proteasome inhibitor, the composition of Adams et al would necessarily inhibits, regulates, or influences a ubiquitin proteasome pathway; influences enzymatic activity of a complete, 26S proteasome complex, or a free, catalytically active 20S proteasome structure not assembled with a regulatory subunit; and be taken up by eukaryotic cells and interacts with a catalytic proteasome subunit for all those properties are inherent of proteasome inhibitors.

It is noted that independent claim 44 is directed to a pharmaceutical formulation and claim 45 depends from claim 44, however, claim 45 (and dependent claims thereof i.e. claims 46-53) contain an intended use recitation "used for the treatment and prophylaxis of HCV-induced hepatitis, flavivirus-induced fever", the cited reference above does not disclose the intended use of the product/composition for the treatment of flavivirus-induced fever; nevertheless a statement of usefulness or contemplated use of a claimed compound or composition in a claim is usually given little weight in distinguishing over the prior art. *In re Maeder et al.* (CCPA 1964) 337 F2d 875, 143 USPQ 248; *In re Riden et al.* (CCPA 1963) 318 F2d 761, 138 USPQ 112; *In re Sinex* (CCPA 1962) 309 F2d 488, 135 USPQ 302. Further, it is well established that the intended use of a compound (e.g., a polypeptide or a protein or a glycoprotein) does not impart patentability to the compound. *In re Spada,* 911 F.2d 705, 15 USPQ2d 1655 (Fed. Cir. 1990) (The discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, can not impart patentability to claims to the known composition); *In re Pearson*, 494 F.2d 1399, 1403, 181 USPQ 641, 644 (CCPA 1974) (intended use of an old composition does not render composition claims patentable); *In re Zierden*, 411 F.2d 1325, 1328, 162 USPQ 102, 104 (CCPA 1969).

Therefore, in the absence of evidence to the contrary or specific structural limitations, the claimed agents intended for treating flavivirus infections thereof as taught by the reference anticipates claims 44-47, 49-51 and 53 as drafted.

CLAIMS REJECTION-35 U.S.C. 102(b)

Claims 44-47 and 49-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Kruger et al (Molecular and Cellular Biology, Vol. 21, No. 24, pp. 8357-8364, December 2001) Cited by Applicant on IDS filed 04/13/06.

The elected claims are drawn to an agent for inhibiting at least one of release, maturation and replication of a member of the *Flavivirdae* family selected from *Flavivirus* wherein the agent comprises, as an active component, at least one proteasome inhibitor in a pharmaceutical preparation (claim 44), wherein the agent is used for the treatment and prophylaxis of HCV-induced hepatitis, falvivirus-induced fever (claim 45), wherein the proteasome inhibitor is a substance which affects the activities of the ubiquitin/proteasome pathway; which specifically affects the enzymatic activities of the complete 26S proteasome complex; and which specifically affects the enzymatic activities of the free 20S catalytically active, proteasome complex, which is not assembled with regulatory subunits (claim 46), wherein the proteasome inhibitor is taken up by higher eukaryotic cells and, after having been taken up into a cell, interacts with the catalytic subunits of the proteasome, and, in connection with this, blocks at least some of the proteolytic activities of the proteasome within the 26S or the 20S proteasome complex (claim 47), wherein the proteasome inhibitor is administered in various mode of administrations as recited in claim 49, wherein the proteasome inhibitor is produced from various sources as recited in claim 50, the derivatives of modified aldehydes such as N-carbobenzoxyl-L-Leucinyl-L-leucinal (designated MG132) (claim 51).

The reference of Kruger et al teaches an agent for inhibiting the 20S proteasome by proteasome inhibitor MG132 exerted a dose-dependent inhibitory effect on HCV IRES (internal ribosome entry site)-mediated translation but not on cap-dependent translation. The data suggest

a principle role for PSMA7 in regulating HCV IRES activity, as a function essential for HCV replication (See abstract and page 8358, left column, first paragraph). On page 8362, right column, second paragraph, the reference investigated whether the observed inhibition of IRES activity can also be achieved by peptide inhibitor the 20S proteasome complex MG132, a potent and selective reversible inhibitor of the 20S proteasome , was administered to HeLa cells stably expressing the simian virus 40-driven bicistronic reporter transcript (RL-5'-CFL) activities were decreased 58 to 81% upon MG132 application. Thus, the data indicate a dose-dependent inhibitory effect of proteasome inhibitor MG132 on HCV IRES activity. Further, on page 8363, right column, third paragraph, the reference shows that the ubiquitin proteasome pathway is highly conserved intracellular pathway for the degradation of proteins. Many of the short-lived regulatory proteins that govern cell division, growth, activation, signaling, and transcription are substrates degraded by the proteasome. The 26S proteasome is a multisubunit protease complex that catalyzes the final step of intracellular protein degradation.

The ubiquinated protein are recognized and unfolded by the regulatory complex and threaded through the small pores at the ends of the catalytic chamber, where they are degraded by different protease activities. The resulting peptides exit from the cylinder, upon which the ubiquitin chains from the degraded protein are recycled. A variety of proteins are processed via the ubiquitin proteasome pathway, such as proteins involved in cell proliferation or cell cycle control, transcriptional regulators, cytosolic proteins, membrane proteins, and major histocompatibility complex class I (MHC-1) antigen processing.

The reference concludes by stating finally, the development of specific, nontoxic, proteasome inhibitors, such as ribozyme, antisense oilgnucleotides, and small molecules that

inhibit active sites of proteasome subunits, might prove useful for investigating the role of the ubiquitin-proteasome pathway in diverse cellular process, such as inflammatory events, cellular immune surveillance, tumorigenesis, and chronic infectious diseases.

It is noted that independent claim 44 is directed to a pharmaceutical formulation and claim 45 depends from claim 44, however, claim 45 (and dependent claims thereof i.e. claims 46-53) contain an intended use recitation "used for the treatment and prophylaxis of HCV-induced hepatitis, flavivirus-induced fever", the cited reference above does not disclose the intended use of the product/composition for the treatment of flavivirus-induced fever; nevertheless a statement of usefulness or contemplated use of a claimed compound or composition in a claim is usually given little weight in distinguishing over the prior art. *In re Maeder et al.* (CCPA 1964) 337 F2d 875, 143 USPQ 248; *In re Riden et al.* (CCPA 1963) 318 F2d 761, 138 USPQ 112; *In re Sinex* (CCPA 1962) 309 F2d 488, 135 USPQ 302. Further, it is well established that the intended use of a compound (e.g., a polypeptide or a protein or a glycoprotein) does not impart patentability to the compound. *In re Spada,* 911 F.2d 705, 15 USPQ2d 1655 (Fed. Cir. 1990) (The discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, can not impart patentability to claims to the known composition); *In re Pearson*, 494 F.2d 1399, 1403, 181 USPQ 641, 644 (CCPA 1974) (intended use of an old composition does not render composition claims patentable); *In re Zierden*, 411 F.2d 1325, 1328, 162 USPQ 102, 104 (CCPA 1969).

Therefore, in the absence of evidence to the contrary or specific structural limitations, the claimed agents intended for treating flavivirus infections thereof as taught by the reference anticipates claims 44-47 and 49-51 as drafted.

Claims 44-47, 49-51 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al (Cell Death and Differentiation, Vol. 5, pp. 577-583, 1998).

The reference of Lin et al tested the proteasome inhibitors MG132 and lactacystin blocked or inhibited Sindbis Virus (SV)-induced apoptosis (See e.g., abstract). Thus, the reference clearly anticipates claims 44-47, 49-51 and 53 as drafted.

Claims 44-47 and 49-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Elliott et al (Am J Clin Pathol, Vol. 116, pp. 637-646, 2001).

The reference of Elliott et al discloses proteasome PS-519 and PS-341 by injection for clinical evaluation of various diseases as recited in the abstract. Figure 1hows the ubiquitin-proteasome pathway which helps define the turnover rates for multiple intracellular proteins. Also, on Table I the reference discloses various naturally and synthetic occurring proteasome inhibitors, for natural occurring such as Lactacystin, Eponemycin, Epoxomycin and Aclacinomycin; for synthetic such as PS-519; MG132 and PS-341. Thus, the reference clearly anticipates claims 44-47 and 49-53 as drafted.

Claims 44-47 and 49-51 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Phillips et al (Stroke, Vol. 31, pp. 1686-1693, 2000).

The reference of Phillips et al examined the *in vivo* neuroprotective efficacy of the 26S proteasome inhibitor PS519 by administering intravenously and its therapeutic role in an early

and late inflammatory response after transient focal brain ischemia in rats (See e.g., under Discussion). Thus, the reference anticipates claims 44-47 and 49-51 and 53 as drafted.

All the above cited references including the reference of Douglas Steinberg (The Scientist, 2001, 15(2):16 (pages 1-7)) and references cited therewith are representative of a large number of references that could have been cited that disclose the known and claimed proteasome inhibitors, and particularly of claim 53.

CLAIM REJECTION-35 U.S.C. 103(a)

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al as applied to claim 44, in view of Cleland et al (U.S. Patent No. 6,913,767).

Claim 49 requires that the composition be in encapsulated form.

As discussed above, the reference of Adams et al teaches the claimed composition. However, Adams et al does not teach the composition in encapsulated form.

The deficiency of Adams et al is compensated by Cleland et al

The patent of Cleland et al teaches a method for delivering a compound to a host in a microsphere format by encapsulating the antigen. [Lines 24-26, column 3]

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to encapsulate the composition of Adams et al One of ordinary skill in the art at the time the invention was made would have been motivated to do so to facilitate the administration of the compound in a microsphere format, e.g. intranasal or mucosal type of administration. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because Cleland et al teaches a method for delivering a compound to a host in a microsphere format by encapsulating the antigen. Thus, absent evidence to the contrary, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for producing the claimed invention.

Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al, Lin et al and/or Elliott et al as applied to claim 44, in view of Liu et al (Biochemistry, Vol. 38, pp. 1415-1425, 1999).

Claim 48 requires that the composition comprises an additional agent which activates of the ubiquitin conjugating enzyme.

As discussed above, the references of Adams et al, Lin et al and/or Elliott et each teaches the claimed composition. However, the primary references cited above do not teach a second agent that effects activities of ubiquitin conjugating enzyme. The deficiency of the primary references is compensated by Liu et al. Liu et al teaches the role of ubiquitination in a variety of biological processes by mainly participates in protein degradation, wherein many crucial proteins are degraded by the ubiquitination pathway (See e.g., page 415, left column, paragraph 2).

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use additionally the process of activating the ubiquitin conjugating enzyme of Liu et al into the composition of the primary references of Adams et al, Lin et al and/or Elliott et al because they each disclose multiple proteasome inhibitors for the same purpose. Thus, in view of the above, the addition of activities of the ubiquitin conjugating enzyme appears to be obvious as taught by the prior art and what is conventional and known in the art at the time the invention was made because one of ordinary would have been motivated to modify the processes taught by the primary references by including an additional components (i.e., ubiquitin conjugating enzyme) taught by Liu et al., since it is not unobvious to combine two or more ingredients or components or compositions which are taught by the prior art to be useful for the same purposes. See *In re Kerhoven*, 205 USPQ 1069 (CCPA 1980). Further, a rejection under 35 U.S.C. § 103 based upon combination of references is not deficient soley because the references are combined based upon a reason of technical consideration which is different from that which resulted in the claimed invention. *Ex parte Raychem Corp*, 17 U.S.P.Q. 2d 1417.

Therefore, absent evidence to the contrary, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for producing the claimed invention.

HEADING FOR NONSTATUTORY DOUBLE PATENTING

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

PROVISIONAL REJECTION OF OBVIOUSNESS TYPE DOUBLE PATENTING

9. Claims 44-53 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 48-68 of copending allowed Application No. 11/732,797. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed invention (Serial No. 10/510,355) as claimed in claims 44-53 is directed to a composition comprising a proteasome inhibitor and a pharmaceutical preparation thereof, wherein the proteasome inhibitor is a boric acid derivative. The claim requires that the inhibitor inhibits, regulates, or influences an ubiquitin proteasome pathway. The claims require that the inhibitor influences enzymatic activity of a complete, 26S proteasome complex, or a free, catalytically active 20S proteasome structure not assembled with a regulatory subunit. The claims also require that the inhibitor be taken up by eukaryotic cells and interacts with a catalytic proteasome subunit, and blocks at least one trypsin, chymotrypsin or postglutamyl peptide-hydrolyzing activity within the 26S or 20S proteasome complex. Additionally, the claims require that the composition be in a form suitable for oral, intravenous, intramuscular or subcutaneous use; the proteasome inhibitor be a naturally occurring substance, a chemically modified natural substance, a synthetic substance, or a substance produced via recombinant means. The claims require that the proteasome inhibitor contains a boric acid radical, which is later limited to dipeptidy Claims 44-47 and 49-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Kruger et al (Molecular and Cellular Biology, Vol. 21, No. 24, pp. 8357-8364, December 2001) Cited by Applicant on IDS filed 04/13/06.l boric acid derivatives, which is further limited to N-pyrazinecarbonyl-L-phenylalanine-L-leucine-boric acid.

Additionally, it is noted that the claims contain an intended use recitation, "useful for treatment and prophylaxis of HCV-induced hepatitis' falvivirus-induced fever, hemorrhages, leucopenia, thrombocytopenia, diarrheal diseases encephalitis or pestivirus-induced diseases. Similarly, claims 48-68 of copending application is directed to a method for treating a hepatitis viral infection by administering the same composition as claimed in claims 44 and 46-53 of the instantly claimed invention.

Although, both inventions are basically the same since they are made by the same procedures using substantially the same materials (i.e., an agent comprising at least one proteasome inhibitor for use in inhibiting at least one of release, maturation and replication of virus) for the purpose of treating viral disease. Nevertheless, the only difference between the two inventions is the scope of the claims. The instantly claimed invention appears to be broader in scope than that of copending application claims, which claims broadly using the same agent for treatment and prophylaxis of HCV-induced hepatitis and other viral diseases with various manifestations and symptoms while the copending application claims specifically a method of treating hepatitis viral infection. Thus, the instant claimed invention intends to treat or prevent (prophylaxis) all kinds of viral diseases as claimed in claim 45, and as such appears to be broader in scope than the copending application claims. However, since both inventions are made by the same procedures using substantially the same materials for the same purposes of treating hepatitis viral infection, it would be within the purview of ordinary skill in the art to use or adapt either the broader scope or the specific because both inventions are obvious variations of the other. Therefore, one pf ordinary skill in the art would envision both sets of claims as one invention and obvious variation of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

CONCLUSION AND FUTURE CORRESPONDANCE

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mohamed/A. A. M./
Examiner, Art Unit 1654

/JON P WEBER/
Supervisory Patent Examiner, Art Unit 1657